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Dietary Carotenoids, Serum β-Carotene, and Retinol and Risk of Lung Cancer in the Alpha-Tocopherol, Beta-Carotene Cohort Study

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Findings from several β-carotene supplementation trials were unexpected and conflicted with most observational studies. Carotenoids other than β-carotene are found in a variety of fruits and vegetables and may play a role in this important malignancy, but previous findings regarding the five major carotenoids are inconsistent. The authors analyzed the associations between dietary β-carotene, β-carotene, lutein/zeaxanthin, lycopene, β-cryptoxanthin, vitamin A, serum β-carotene, and serum retinol and the lung cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of male smokers conducted in southwestern Finland between 1985 and 1993. Of the 27,084 male smokers aged 50–69 years who completed the 276-food item dietary questionnaire at baseline, 1,644 developed lung cancer during up to 14 years of follow-up. Cox proportional hazards models were used to estimate relative risks and 95% confidence intervals. Consumption of fruits and vegetables was associated with a lower lung cancer risk (relative risk = 0.73, 95% confidence interval: 0.62, 0.86, highest vs. lowest quintile). Lower risks of lung cancer were observed for the highest versus the lowest quintiles of lycopene (28%), lutein/zeaxanthin (17%), β-cryptoxanthin (15%), total carotenoids (16%), serum β-carotene (19%), and serum retinol (27%). These findings suggest that high fruit and vegetable consumption, particularly a diet rich in carotenoids, tomatoes, and tomato-based products, may reduce the risk of lung cancer. *Am J Epidemiol* 2002;156:536–47.

beta-carotene; carotenoids; lung neoplasms; prospective studies; vitamin A

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene; CI, confidence interval; RR, relative risk.

Lung cancer incidence and mortality have increased sharply in the last century, making it a leading cause of death and the most common malignant tumor worldwide (1). Despite the observed decrease in incidence in the United States since the late 1980s, 169,400 new cases of lung cancer are estimated to occur in 2002 (2). Although the principal cause is tobacco use, epidemiologic studies across many different populations, subgroups, and study designs have shown that lung cancer risk is inversely associated with the intake of carotenoid-containing fruits and vegetables after potential confounding by smoking habits is taken into account (3–5).

The six carotenoids found in the highest concentrations in human serum are β-carotene, α-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin (6). The mechanisms for the cancer-preventing actions of carotenoids observed in animal models are not known (7) but may involve antioxidant activity, stimulation of gap junction intercellular communication, induction of detoxifying enzymes, and inhibition of cellular proliferation (8). As a result of such potential anticarcinogenic properties, it has been speculated that carotenoids play a role in the prevention of lung and other cancers.

Hypothesized to be one of the promising active compounds in fruits and vegetables, β-carotene has been studied extensively, both prospectively and retrospectively. Results from observational studies have shown a consistent association of increased lung cancer risk with low dietary β-

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carotene or serum β-carotene concentrations (9–12). However, three large intervention trials initiated in the 1980s to evaluate the potential of β-carotene supplements in the prevention of lung and other cancers failed to confirm this relation (13–15). Results from two trials in high-risk populations reported an increased risk of lung cancer after β-carotene supplementation (13, 14), and the third trial reported no significant effect of β-carotene on the incidence of lung or other cancers (15). In contrast, two of the trials observed an inverse association between baseline dietary intake and serum levels of β-carotene and subsequent risk of lung cancer among current and former smokers (13, 14). On the basis of these inconsistencies between trial and observational study results, questions have arisen concerning the potential difference between dietary and supplemental β-carotene. The possibility of a smoke-related, harmful effect of β-carotene supplementation has been suggested (16) in addition to the speculation that carotenoids other than β-carotene, or a combination of carotenoid intakes, contribute to the associations observed with lung cancer (17).

Recent studies that have addressed the association between individual carotenoid intake and lung cancer risk have been inconsistent. Using a newly available food composition carotenoid database established by the US Department of Agriculture-National Cancer Institute, two population-based case-control studies observed a significant inverse trend in lung cancer risk for intakes of β-carotene (10, 18). In contrast to these findings, a hospital-based case-control study (19) and additional prospective studies (20–22) have reported inverse, but not statistically significant, associations between dietary β-carotene and lung cancer risk. In the same studies, significant associations were also observed for lutein/zeaxanthin (10), α-carotene (10, 18, 20, 21), and lycopene (21). Our study examines the relation between baseline dietary and serum carotenoids and lung cancer risk in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study**.** The ATBC Study population provides a unique opportunity to examine these associations because of its extended follow-up, detailed dietary data collected at baseline, availability of serum β-carotene and retinol measures, and 1,644 cases of incident lung cancer.

MATERIALS AND METHODS

Study design and subjects

The ATBC Cancer Prevention Study was a randomized, double-blind, placebo-controlled, 2 × 2 factorial-design, chemoprevention trial of male smokers conducted between 1985 and 1993 in southwestern Finland. The primary objective of the study was to evaluate the effects of supplemental vitamin E and β-carotene on the incidence of lung and other major cancers (23). In all, 29,133 White males aged 50–69 years who smoked five or more cigarettes per day were randomized in 1985–1988 to receive a daily dose of *dl*-alpha-tocopherol (50 mg), β-carotene (20 mg), both, or a placebo. Exclusion criteria included history of malignancy other than nonmelanoma cancer of the skin or carcinoma in situ, severe angina on exertion, chronic alcoholism, cirrhosis of the liver, chronic renal insufficiency, and other medical problems that might limit long-term participation; receiving anticoagulant therapy; taking supplements with vitamin A (>20,000 IU/day), vitamin E (>20 mg/day) or β-carotene (>6 mg/day); or lung cancer detected on a prerandomization chest film (23). The trial ended on April 30, 1993, with passive case ascertainment for this study continuing thereafter until death or through December 1998, representing follow-up data for up to 14 years (median, 11 years). The institutional review boards of both the National Public Health Institute of Finland and the US National Cancer Institute approved the study, and written, informed consent was obtained from each participant before randomization.

Data collection

At baseline, participants completed questionnaires that assessed information on medical, smoking, and dietary histories. Physical measurements included height, weight, and a chest x-ray. Serum samples were obtained from participants who had been fasting for up to 12 hours; the samples were then frozen at –70°C (23). Baseline serum concentrations of β-carotene and retinol were measured from thawed samples by using reverse-phase, high-performance liquid chromatography with isocratic elution (24). Information on smoking cessation was gathered at three annual follow-up visits.

Dietary information was gathered by using a self-administered food-use questionnaire given to all participants before randomization. The diet history questionnaire developed specifically for the ATBC Study used a color picture booklet as an aid and asked participants to report their usual frequency of consumption and portion during the previous year for more than 270 common food items and beverages. The questionnaire's correlation coefficients for validity using food records and reliability ranged from 0.40 to 0.80 and from 0.56 to 0.88, respectively (25). Data on dietary carotenoid and retinol intakes were based primarily on food composition tables developed from high-performance liquid chromatography analyses of Finnish foods (26–30). Complete dietary data were available for 27,111 participants. Dietary nutrient intake was estimated by linking foods from the dietary history questionnaire to food composition data available from the National Public Health Institute of Finland.

Case ascertainment

Incident lung cancer cases were identified through the nationwide Finnish Cancer Registry and the Register of Causes of Death (23). To enhance the ascertainment of cases, we obtained a chest film every 28 months for the duration of the trial and at each participant's exit from the trial. Medical records were obtained for identified cases and were reviewed centrally by one or two study physicians. Histologic or cytologic confirmation was achieved for 93 percent of the cases. A total of 1,644 cases diagnosed between randomization and December 31, 1998, were included in this report.

Statistical analyses

Follow-up time for each subject was calculated from the date of randomization until the date of lung cancer diagnosis,

date of death, or December 31, 1998, whichever came first. Only those with complete dietary and smoking history and serum β-carotene and retinol measurements were included in the analyses (n = 27,084 persons and 279,201 person-years). Cox proportional hazards models were used to estimate relative risks and 95 percent confidence intervals for dietary β-carotene, α-carotene, lycopene, lutein/zeaxanthin, β-cryptoxanthin, retinol, total vitamin A, serum β-carotene, and serum retinol.

Spearman correlations were performed to assess the collinearity among covariates. Potential confounders were specified a priori based on a review of putative risk factors for lung cancer and included age; education (primary, high school, vocational, and university); area of residence (small town (<50,000 inhabitants) and large town (>50,000 inhabitants)); marital status; body mass index (kg/m^2); dietary vitamin C, fat, and cholesterol; serum total cholesterol; and vitamin A or β-carotene supplement intake before randomization (yes/no). Smoking history was assessed by age (year) the participant started to smoke regularly; number of years smoked regularly; average total number of cigarettes smoked daily (intensity); smoking inhalation (never/seldom, always/often); and smoking cessation (never or ever having quit smoking for at least three consecutive visits (i.e., 1 year) during the trial). Calorie adjustment was performed for all dietary nutrients according to the residual method (31).

Dietary intake and serum nutrients were classified into quintiles or deciles based on the distribution of the entire cohort, and additional covariates were modeled as continuous or categorical variables. A small number of men (<1 percent of the cases) reported consuming nutrient supplements at baseline but at levels that did not exclude them from participating. To address this, we ran age-adjusted models that included controlling for supplement use, excluding supplement users, and creating a variable that combined dietary and supplement use for β-carotene and total vitamin A. Multivariate models included age, energy intake, smoking history (duration and intensity), intervention (α-tocopherol and β-carotene supplement), supplement use (β-carotene and vitamin A), and additional secondary confounders that were assessed by evaluating whether their inclusion in the multivariate model changed the risk estimate by more than 10 percent. Additional models adjusted for fruit and vegetable intake. To assess potential interaction, analyses were stratified by histologic type (adenocarcinoma, small cell carcinoma, squamous cell carcinoma, and all other types), alcohol intake (median split, ≥11 g of ethanol per day (just under one drink per day)), fruit and vegetable intake, and cigarettes per day. Interaction was tested by including the factor of interest (with the exception of histologic subtype) and its cross-product term in multivariate models. Linear trends were tested by fitting a term taking the median values of each quintile of dietary intake or serum concentration. Proportional hazards assumptions were tested by using lagged analysis and an interaction term with time. Relative risks were computed for each of the quintiles by dividing the rates in the upper quintiles of intake by the rates in the lowest category of intake. All reported p values are two-tailed. Statistical analyses were performed using SAS software version 8.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Men with greater dietary carotenoid intake and serum β-carotene levels tended to have a higher intake of fruits and vegetables, a lower number of years smoking, and a lower dose of smoke (cigarettes per day) and were more likely to quit smoking during the trial than were men with lower carotenoid exposure (table 1). Regardless of total carotenoid intake or serum β-carotene level, primary school was the highest education attained by more than half of the cohort participants, and low carotenoid intake was associated with the lowest education levels (e.g., fewer than 2 percent had a university education). Similar trends were observed across the same categories of smoking history and education level for tertile of fruit and vegetable intake (data not shown).

In age-adjusted proportional hazards models, significant inverse associations were observed for each of the individual dietary carotenoids (table 2). These associations were attenuated after adjustment for potential risk factors, with nearly all of the difference being accounted for by smoking duration and intensity. From the multivariate models, participants who consumed high quantities compared with low quantities of lycopene, lutein/zeaxanthin, β-cryptoxanthin, and total carotenoids were observed to have a significant 15–28 percent lower lung cancer risk ($p < 0.05$; table 2). High intakes of β-carotene, α-carotene, and retinol were not associated with risk, and similar results were found for dietary total vitamin A (data not shown). Serum β-carotene and retinol levels were both inversely related to the risk of lung cancer, even after adjustment for cigarette smoking. Similar multivariate relative risks for individual carotenoid intakes and lung cancer risk were observed in the placebo group alone.

We further stratified dietary intakes and serum concentrations into deciles to examine trends, and a dose-dependent association was observed for lycopene intake. The multivariate relative risks of lung cancer by increasing lycopene decile were 1.00, 0.96, 0.96, 0.85, 0.99, 0.84, 0.77, 0.78, 0.72, and 0.68 (95 percent confidence interval (CI) for highest decile: 0.54, 0.85, $p < 0.0001$). For all dietary and serum components, relative risks were proportional over time.

Because dietary carotenoids are correlated, with correlation coefficients ranging between 0.21 and 0.53 in this population, we modeled α-carotene, lycopene, lutein/zeaxanthin, and β-cryptoxanthin simultaneously, adjusting for other potential confounders, to determine whether the reported associations with dietary carotenoids were independent of each other. We were unable to dissociate the independent effects of β-carotene and α-carotene intakes because they were highly correlated (r = 0.99). We observed significant independent associations for intakes of lycopene and lutein/zeaxanthin, but not for α-carotene or β-cryptoxanthin (p values for continuous variables = 0.0003, 0.04, 0.10, and 0.51, respectively).

Adjustment for fruit and vegetable intake in the multivariate analyses attenuated the risk estimates of the dietary and serum carotenoids by 7–19 percent, with the exception of lycopene and serum retinol (relative risk (RR) = 0.77, 95 percent CI: 0.64, 0.92 and RR = 0.73, 95 percent CI: 0.62,

TABLE 1. Baseline characteristics* (medians and proportions) by dietary total carotenoid intake and serum beta-carotene level in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985–1998

Characteristics	Quintile of total carotenoid intake (μg/day)			Quintile of serum β-carotene level (μg/liter)		
	1 (<2,770)	3 (3,787–4,988)	5 (>6,792)	1 (<99)	3 (148–201)	5 (>290)
No. of participants	5,416	5,417	5,417	5,383	5,441	5,435
Age (years)	57.9	57.1	56.7	56.9	57.2	57.3
Height (cm)	173	174	175	173	174	174
Body mass index (kg/m^2)	26.0	26.3	26.3	26.8	26.3	25.3
Diet						
Fruits and vegetables (g/day)	108	219	390	193	231	274
Cholesterol (mg/day)†	538	574	562	565	564	556
Fat (g/day)†	120	119	115	116	120	120
Serum cholesterol (mmol/liter)	6.3	6.2	6.2	5.8	6.3	6.6
Smoking history						
Cigarettes/day	21.7	20.4	19.3	22.1	20.5	18.9
No. of years smoked	36.7	36.0	35.3	36.6	35.9	35.4
Pack-years	40.1	36.9	34.4	40.6	36.9	33.8
Age started smoking (years)	19.1	19.4	19.9	19.1	19.5	19.8
Smoking inhalation (%)						
Never/seldom	8	8	11	8	9	10
Always/often	92	92	89	92	91	90
Smoking cessation‡ (%)	12	15	20	11	17	21
Education level (%)						
Primary	74	65	54	66	66	61
High school	6	7	9	9	7	8
Vocational	18	24	29	22	23	26
University	2	4	8	4	4	6
Area of residence (%)						
Small town	61	58	53	54	60	57
Large town	39	42	47	47	41	43
Disease history (%)						
Bronchial asthma	3.7	3.0	2.7	3.5	2.8	3.0
Lung emphysema	7.1	7.0	5.5	6.4	6.8	6.7
Chronic bronchitis	7.8	7.2	8.0	9.2	7.3	6.9

* Adjusted for age.
† Adjusted for energy intake.
‡ Quit smoking for at least 1 year during the trial.

TABLE 2. Relative risk of lung cancer according to categories of baseline dietary carotenoid intake and serum β-carotene and retinol level in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985–1998

Quintile of nutrient (per day)	Median intake	No. of cases	No. of person-years	Age-adjusted		Multivariate*	
				RR†	95% CI†	RR	95% CI
β-Carotene (μg)							
1 (<977)	735	390	53,890	1.00	Reference	1.00	Reference
2 (977–1,440)	1,207	340	55,365	0.89	0.77, 1.03	0.92	0.79, 1.06
3 (1,441–2,029)	1,713	330	55,987	0.84	0.73, 0.98	0.90	0.78, 1.04
4 (2,030–3,015)	2,448	271	57,080	0.70	0.60, 0.82	0.79	0.68, 0.92
5 (>3,015)	4,052	313	56,879	0.80	0.69, 0.93	0.92	0.79, 1.07
				p for trend‡= 0.002		*p* for trend‡ = 0.24	
α-Carotene (μg)							
1 (<180)	106	392	54,138	1.00	Reference	1.00	Reference
2 (180–346)	259	326	55,390	0.85	0.74, 0.99	0.89	0.77, 1.03
3 (347–571)	446	334	56,284	0.85	0.74, 0.98	0.94	0.81, 1.09
4 (572–949)	728	289	56,537	0.75	0.64, 0.87	0.82	0.70, 0.95
5 (>949)	1,363	303	56,852	0.77	0.66, 0.89	0.94	0.81, 1.09
				p for trend‡ = 0.001		*p* for trend‡ = 0.47	
Lycopene (μg)							
1 (<232)	112	411	53,370	1.00	Reference	1.00	Reference
2 (232–466)	345	367	54,551	0.92	0.80, 1.05	0.93	0.81, 1.07
3 (467–735)	593	338	56,301	0.86	0.74, 0.99	0.93	0.81, 1.08
4 (736–1,168)	916	292	56,849	0.76	0.66, 0.89	0.79	0.68, 0.92
5 (>1,168)	1,589	236	58,130	0.63	0.54, 0.75	0.72	0.61, 0.84
				p for trend‡ < 0.0001		*p* for trend‡ < 0.0001	
Lutein/zeaxanthin (μg)							
1 (<1,012)	853	408	53,301	1.00	Reference	1.00	Reference
2 (1,012–1,254)	1,139	331	55,599	0.83	0.71, 0.95	0.95	0.82, 1.10
3 (1,255–1,496)	1,374	334	56,133	0.85	0.73, 0.98	0.88	0.76, 1.02
4 (1,497–1,815)	1,637	293	56,722	0.75	0.64, 0.87	0.77	0.66, 0.91
5 (>1,815)	2,106	278	57,446	0.74	0.64, 0.86	0.83	0.71, 0.99
				p for trend‡ < 0.0001		*p* for trend‡ = 0.006	
β-Cryptoxanthin (μg)							
1 (<5)	2	380	54,610	1.00	Reference	1.00	Reference
2 (5–14)	10	343	55,337	0.94	0.82, 1.09	0.94	0.81, 1.09
3 (15–27)	21	331	56,389	0.91	0.78, 1.05	1.00	0.86, 1.15
4 (28–56)	39	311	56,611	0.86	0.74, 1.00	0.93	0.80, 1.08
5 (>56)	73	279	56,254	0.78	0.67, 0.91	0.85	0.72, 0.99
				p for trend‡ = 0.001		*p* for trend‡ = 0.04	

Table continues

0.86 for the highest compared with the lowest quintiles of lycopene and retinol, respectively; data not shown). Similarly, adjustment for vitamin C intake attenuated the relative risk for dietary β-carotene, α-carotene, lutein/zeaxanthin, β-cryptoxanthin, carotenoids, total vitamin A, and serum β-carotene by 2–9 percent but made no difference for lycopene and serum retinol.

To reduce potential bias from the influence of preclinical cancer on baseline dietary intakes or serum concentrations, we conducted additional analyses that excluded all cases of

TABLE 2. Continued

Quintile of nutrient (per day)	Median intake	No. of cases	No. of person-years	Age-adjusted		Multivariate*	
				RR	95% CI	RR	95% CI
Carotenoids (μg)							
1 (<2,770)	2,170	397	53,561	1.00	Reference	1.00	Reference
2 (2,770–3,786)	3,281	364	55,136	0.94	0.82, 1.08	0.98	0.85, 1.14
3 (3,787–4,988)	4,344	320	56,109	0.80	0.69, 0.93	0.88	0.76, 1.02
4 (4,989–6,792)	5,777	276	56,921	0.70	0.60, 0.81	0.78	0.67, 0.92
5 (>6,792)	8,577	287	57,474	0.72	0.62, 0.84	0.84	0.72, 0.99
				p for trend‡ < 0.0001		*p* for trend‡ = 0.005	
Retinol (μg)							
1 (<717)	545	325	54,865	1.00	Reference	1.00	Reference
2 (717–1,044)	875	346	55,097	1.07	0.92, 1.25	0.97	0.83, 1.14
3 (1,045–1,481)	1,247	344	55,710	1.09	0.93, 1.27	1.02	0.87, 1.20
4 (1,482–2,138)	1,768	319	56,550	1.03	0.88, 1.20	1.03	0.88, 1.21
5 (>2,138)	2,768	310	56,979	1.01	0.86, 1.18	0.96	0.82, 1.13
				p for trend‡ = 0.69		*p* for trend‡ = 0.73	
Serum β-carotene (μg/liter)							
1 (<99)	72	384	52,807	1.00	Reference	1.00	Reference
2 (99–147)	122	344	55,039	0.82	0.71, 0.95	0.88	0.76, 1.02
3 (148–201)	171	315	56,369	0.74	0.64, 0.86	0.82	0.71, 0.96
4 (202–290)	238	302	56,822	0.70	0.60, 0.81	0.81	0.70, 0.95
5 (>290)	385	299	58,164	0.66	0.57, 0.77	0.81	0.69, 0.95
				p for trend‡ < 0.0001		*p* for trend‡ = 0.02	
Serum retinol (μg/liter)							
1 (<484)	438	407	53,527	1.00	Reference	1.00	Reference
2 (484–547)	517	367	55,562	0.91	0.79, 1.05	0.93	0.81, 1.08
3 (548–607)	577	334	56,904	0.85	0.73, 0.98	0.89	0.77, 1.03
4 (608–684)	641	288	56,698	0.75	0.65, 0.87	0.80	0.68, 0.93
5 (>684)	753	248	56,510	0.68	0.58, 0.80	0.73	0.62, 0.86
				p for trend‡ < 0.0001		*p* for trend‡ < 0.0001	

* Proportional hazards models include adjustment for age, years smoked, cigarettes per day, intervention (α-tocopherol and β-carotene supplement), supplement use (β-carotene and vitamin A), energy intake, cholesterol, and fat. For serum multivariate models, adjustments are identical minus the dietary components (energy intake, cholesterol, and fat) but including serum cholesterol.

† RR, relative risk; CI, confidence interval.

‡ Two-sided *p* for trend.

lung cancer diagnosed within the first 4 years after randomization. The results, based on 1,207 cases, were similar to those presented in table 2 (e.g., highest compared with lowest quintile of serum retinol, RR = 0.76, 95 percent CI: 0.63, 0.92; and of lycopene, RR = 0.73, 95 percent CI: 0.60, 0.87).

Total fruit, total vegetable, and total fruit and vegetable intakes were associated with a significantly lower risk of lung cancer, with some attenuation in the multivariate models (table 3). We further evaluated fruits and vegetables containing carotenoids and identified the foods that contributed the most to the dietary carotenoid intakes. As expected, the top contributor of β-carotene and α-carotene intakes was carrots, and the main source of lycopene intake was tomatoes. Citrus fruits (i.e., orange, mandarin, and grapefruit) were the primary contributors of β-cryptoxanthin. Rye bread was an important source of lutein/zeaxanthin in this population (28). To determine which of the foods contributing to carotenoid intake were significant predictors of lung cancer risk, stepwise regression was performed. Of the approximately 20 foods contributing to the usual dietary carotenoids, low intakes of tomatoes/tomato juice, lettuce-cucumber-tomato salad, and Chinese cabbage-cucumber-

TABLE 3. Relative risk of lung cancer according to categories of baseline fruit and vegetable intake in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985–1998

Quintile of intake (per day)	Median intake	No. of cases	Age-adjusted		Multivariate*	
			RR†	95% CI†	RR	95% CI
Fruits (g)						
1 (<45)	25	397	1.00	Reference	1.00	Reference
2 (45–84)	65	356	0.87	0.76, 1.01	1.00	0.86, 1.16
3 (85–126)	105	321	0.78	0.67, 0.90	1.00	0.87, 1.16
4 (127–188)	152	297	0.71	0.61, 0.83	0.82	0.70, 0.96
5 (>188)	245	273	0.67	0.57, 0.78	0.87	0.74, 1.02
			p for trend‡ < 0.0001		*p* for trend‡ = 0.01	
Vegetables (g)						
1 (<52)	36	405	1.00	Reference	1.00	Reference
2 (52–79)	66	372	0.93	0.81, 1.07	1.00	0.87, 1.16
3 (80–109)	94	328	0.82	0.71, 0.95	0.93	0.80, 1.08
4 (110–156)	130	288	0.73	0.63, 0.85	0.83	0.71, 0.96
5 (>156)	197	251	0.66	0.56, 0.77	0.75	0.63, 0.88
			p for trend‡ < 0.0001		*p* for trend‡ < 0.0001	
Fruits and vegetables (g)						
1 (<116)	80	407	1.00	Reference	1.00	Reference
2 (116–176)	147	362	0.88	0.76, 1.02	0.91	0.79, 1.05
3 (177–241)	207	326	0.79	0.68, 0.91	0.95	0.82, 1.10
4 (242–332)	280	293	0.71	0.61, 0.83	0.82	0.71, 0.96
5 (>332)	415	256	0.64	0.55, 0.75	0.73	0.62, 0.86
			p for trend‡ < 0.0001		*p* for trend‡ < 0.0001	

* Proportional hazards models include adjustment for age, years smoked, cigarettes per day, intervention (α-tocopherol and β-carotene supplement), supplement use (β-carotene and vitamin A), energy intake, cholesterol, and fat.
† RR, relative risk; CI, confidence interval.
‡ Two-sided *p* for trend.

tomato salad were most strongly associated with lung cancer ($p < 0.05$).

No evidence of an interaction was observed between low (<207 g/day) and high (≥207 g/day) fruit and vegetable intake and the dietary carotenoids, retinol, serum β-carotene, or serum retinol for lung cancer risk (data not shown). In addition, we found no evidence of an interaction between the trial β-carotene or α-tocopherol supplementation or alcohol intake and any of the carotenoids studied (p for interaction > 0.05; data not shown).

The associations between lung cancer risk and the dietary carotenoids, retinol, serum β-carotene, and serum retinol were not materially modified by the number of cigarettes smoked daily (p for interaction > 0.05; table 4). For example, inverse associations were observed for lycopene intake and risk of lung cancer across all three groups of smoking intensity ($p < 0.05$ in each group). For total carotenoid intake, a stronger inverse association was suggested among men who smoked 30 cigarettes or more per day than in the other two groups of smokers. Among men who smoked 5–19 cigarettes per day, a significant inverse trend with serum β-carotene and lung cancer risk was observed ($p = 0.02$) that was not seen among heavier smokers

Evaluation of histologic subtypes showed that dietary lutein/zeaxanthin, α-carotene, and β-carotene were not associated with risk of adenocarcinoma (256 cases), small cell carcinoma (362 cases), squamous cell carcinoma (684 cases), or other carcinomas combined (269 cases) (data not shown). Lycopene showed significant inverse associations with risk of small cell, squamous cell, and other carcinomas, but not adenocarcinoma. β-Cryptoxanthin and total carotenoids showed significant inverse associations with squamous cell carcinoma only.

DISCUSSION

Among the dietary carotenoids, we observed significant inverse associations between lycopene, lutein/zeaxanthin, β-cryptoxanthin, and total carotenoids and risk of any type of lung cancer in this prospective study of male smokers. Intakes of β-carotene, α-carotene, and retinol were not significantly associated with risk, whereas serum β-caro-

tene and serum retinol showed significant inverse relations, even after controlling for smoking. Lycopene and lutein/zeaxanthin were independently associated with lung cancer risk in a multivariate model that included α-carotene, lycopene, lutein/zeaxanthin, and β-cryptoxanthin simultaneously. Consumption of fruits and vegetables was also significantly inversely associated with lung cancer risk.

Previous observational studies examined the relation between individual dietary carotenoids and the risk of lung cancer, but findings have not been entirely consistent. Results from studies using recently updated carotenoid databases have observed inverse associations for at least one of the five common carotenoids (10, 18–22, 32). Our results are consistent with the idea that carotenoids other than β-carotene, or a combination of carotenoids, may have the potential for lung cancer prevention.

In a random sample of 1,000 men in the ATBC cohort, we evaluated foods that made the greatest contribution to estimated usual dietary intakes of carotenoids. For β-carotene, α-carotene, lycopene, lutein/zeaxanthin, and β-cryptoxanthin, a minimum of three or a maximum of 10 food sources predicted 75 percent of the individual carotenoid intake. We were limited by the number and types of fruits and vegetables consumed by the ATBC cohort, due to the fewer and different sources of carotenoids compared with what is traditionally found in the US diet. For example, lutein/zeaxanthin is most commonly consumed in foods such as broccoli, kale, and spinach in the United States (33), whereas the top food sources of lutein/zeaxanthin in this Finnish population included whole-grain rye bread, eggs, a combination of vegetables (e.g., cucumber, lettuce, and potato), and pea soup. For the other carotenoids—β-carotene, α-carotene, lycopene, and β-cryptoxanthin—the top food sources were similar to US food sources (33) and included carrots, tomatoes, and citrus fruits (i.e., orange, mandarin, and grapefruit), respectively. Among the food groups that contributed the most to the dietary carotenoids, the strongest lung cancer associations were observed for tomatoes, lettuce-cucumber-tomato salad, and Chinese cabbage-cucumber-tomato salad. In addition to the limited number and types of fruits and vegetables, the average dietary carotenoid intake in the ATBC cohort was lower than that in the United States as reported by the National Health and Nutrition Examination Surveys (1988–1994) (e.g., median daily intake of lycopene in the ATBC was 590 μg vs. 6,879 μg in the Third National Health and Nutrition Examination Survey for men aged 51–70 years) (34).

Few foods on the food frequency questionnaire captured dietary lycopene in this cohort, which is reflected by the low lycopene values. Estimates of lycopene intake were based primarily on raw tomatoes and tomato juice. A previous study has indicated that lycopene is more bioavailable in cooked than in raw products (35). In a separate analysis of ATBC data, we modeled pasta as a surrogate for the more bioavailable sources of lycopene intake, and an inverse association with lung cancer risk was observed. Previous studies have found significant inverse trends with tomato intake and lung cancer risk (10, 36–38), and others have found inverse, but nonsignificant, associations (9, 39, 40). Of the two studies that looked at lycopene and tomato intake simultaneously, one found a significant inverse association for tomato intake and an inverse, but nonsignificant, association for lycopene intake and risk of lung cancer (10); the other found nonsignificant inverse associations for both lycopene and tomato intake (39). It is possible that the association of lycopene is confounded by other compounds in tomatoes (including the phenolic compounds coumaric acid and chlorogenic acid (41) and the colorless carotenoids phytoene and phytofluene (42)) that may be important in reducing lung cancer risk. However, the low correlation of lycopene with the other dietary carotenoids (r = 0.2–0.4) in these data, along with the stronger risk estimate for lycopene intake compared with those for total fruit and vegetable intake, support a role for tomatoes/tomato-based products and possibly for lycopene as an independent predictor of lung cancer.

In the original publications from the ATBC Study (23, 43), inverse associations were reported between dietary β-carotene intake at baseline and lung cancer incidence in the unsupplemented group (incidence rate per 100,000 person-years for the highest and lowest dietary β-carotene quartiles, 466 and 536) (43). In our analysis, based on extended follow-up, null results were found between dietary β-carotene at baseline and lung cancer risk in the placebo and supplemented groups. This study reports results based on more than 1,644 incident lung cancer cases, almost double the number observed in the original publications (876 cases (23) and 894 cases (43)). The most likely explanation for these differences is that the rates in the first publication were age adjusted only (23), and in the second paper, they were adjusted for age and number of cigarettes (43) compared with our results from multivariate analyses (controlling for other potential confounders and smoking duration).

We observed significant inverse associations between lung cancer risk and serum concentrations of β-carotene and retinol, but not dietary β-carotene or retinol (44, 45). While it is possible that circulating levels are the more relevant biologic exposure, other factors could account for the pattern. Dietary retinol and β-carotene and their respective serum markers are only weakly correlated in our study (retinol, r = 0.05; β-carotene, r = 0.22), similar to that observed by others (44–47), and low serum retinol concentrations, in particular, are not specific to poor retinol status (48). Serum retinol is known to decrease during infection and chronic inflammation (49–51), and infectious disease may deplete vitamin A stores by accelerating metabolic losses, impairing intestinal absorption, or both (52). In addition, the changes in serum retinol may be induced by proinflammatory cytokines due to the acute-phase response (51, 52). Recently, serum β-carotene was also strongly and inversely related to markers of inflammation, C-reactive protein, and white blood cell counts among healthy participants in the Third National Health and Nutrition Examination Survey (53). The inability to adjust for confounding by inflammatory markers, which are potential risk factors for lung cancer, may have confounded the results. Therefore, the inconsistency between the dietary and serum results might be explained by low concentrations of these nutrients due to the presence of inflammation in the body. Alternatively, the

TABLE 4. Relative risk of lung cancer according to categories of baseline dietary intake and serum level by baseline cigarettes per day in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985–1998

Quintile of nutrient (per day)	Median intake	Cigarettes/day								
		5–19			20–29			≥30		
		No. of cases	Multivariate*		No. of cases	Multivariate*		No. of cases	Multivariate*	
			RR†	95% CI†		RR	95% CI		RR	95% CI
β-Carotene (μg)										
1 (<977)	735	91	1.00	Reference	184	1.00	Reference	114	1.00	Reference
2 (977–1,440)	1,207	85	0.86	0.64, 1.16	172	1.01	0.82, 1.24	79	0.82	0.61, 1.09
3 (1,441–2,029)	1,713	72	0.66	0.49, 0.90	180	1.10	0.89, 1.35	77	0.83	0.62, 1.10
4 (2,030–3,015)	2,448	93	0.83	0.62, 1.11	136	0.87	0.69, 1.08	46	0.59	0.42, 0.84
5 (>3,015)	4,052	115	0.91	0.69, 1.20	142	0.99	0.79, 1.23	58	0.83	0.60, 1.14
			p for trend‡ = 0.90			*p* for trend‡ = 0.57			*p* for trend‡ = 0.14	
α-Carotene (μg)										
1 (<180)	106	94	1.00	Reference	189	1.00	Reference	114	1.00	Reference
2 (180–346)	259	78	0.77	0.57, 1.05	166	0.98	0.80, 1.21	75	0.83	0.62, 1.12
3 (347–571)	446	71	0.65	0.48, 0.88	182	1.14	0.93, 1.40	80	0.91	0.69, 1.22
4 (572–949)	728	96	0.83	0.63, 1.11	134	0.87	0.69, 1.08	48	0.67	0.48, 0.94
5 (>949)	1,363	117	0.90	0.68, 1.18	143	1.00	0.80, 1.24	57	0.87	0.63, 1.20
			p for trend‡ = 0.69			*p* for trend‡ = 0.65			*p* for trend‡ = 0.30	
Lycopene (μg)										
1 (<232)	112	117	1.00	Reference	192	1.00	Reference	103	1.00	Reference
2 (232–466)	345	88	0.73	0.56, 0.97	192	1.10	0.90, 1.34	76	0.86	0.64, 1.15
3 (467–735)	593	95	0.80	0.61, 1.05	179	1.08	0.88, 1.32	73	0.84	0.62, 1.13
4 (736–1,168)	916	80	0.71	0.53, 0.94	134	0.84	0.67, 1.05	69	0.81	0.60, 1.11
5 (>1,168)	1,589	76	0.65	0.49, 0.87	117	0.81	0.64, 1.02	53	0.63	0.45, 0.88
			p for trend‡ = 0.01			*p* for trend‡ = 0.009			*p* for trend‡ = 0.008	
Lutein/zeaxanthin (μg)										
1 (<1,012)	853	94	1.00	Reference	202	1.00	Reference	95	1.00	Reference
2 (1,012–1,254)	1,139	98	0.93	0.70, 1.24	175	0.92	0.75, 1.13	81	1.03	0.76, 1.39
3 (1,255–1,496)	1,374	83	0.78	0.58, 1.06	161	0.89	0.72, 1.10	73	0.99	0.73, 1.35
4 (1,497–1,815)	1,637	83	0.69	0.51, 0.94	137	0.80	0.64, 1.00	59	0.87	0.62, 1.22
5 (>1,815)	2,106	98	0.89	0.65, 1.21	139	0.81	0.64, 1.04	66	0.83	0.58, 1.19
			p for trend‡ = 0.24			*p* for trend‡ = 0.05			*p* for trend‡ = 0.21	
β-Cryptoxanthin (μg)										
1 (<5)	2	96	1.00	Reference	192	1.00	Reference	102	1.00	Reference
2 (5–14)	10	88	0.99	0.74, 1.32	162	0.91	0.74, 1.13	79	0.91	0.68, 1.22
3 (15–27)	21	111	1.12	0.85, 1.47	160	1.02	0.83, 1.26	68	0.82	0.60, 1.12
4 (28–56)	39	80	0.82	0.61, 1.11	162	1.00	0.81, 1.24	64	0.90	0.65, 1.23
5 (>56)	73	81	0.78	0.58, 1.05	138	0.91	0.73, 1.13	61	0.83	0.60, 1.14
			p for trend‡ = 0.03			*p* for trend‡ = 0.57			*p* for trend‡ = 0.33	

Table continues

differences between dietary and serum nutrient risk estimates could be accounted for by measurement error in dietary assessment, with biochemical assays offering more accurate nutritional assessment of β-carotene.

The differences between the age-adjusted and multivariate relative risks of lung cancer for the dietary carotenoids, retinol, serum β-carotene, and serum retinol were primarily the result of confounding by smoking history. To minimize confounding

TABLE 4. Continued

Quintile of nutrient (per day)	Median intake	Cigarettes/day								
		5–19			20–29			≥30		
		No. of cases	Multivariate*		No. of cases	Multivariate*		No. of cases	Multivariate*	
			RR	95% CI		RR	95% CI		RR	95% CI
Carotenoids (μg)										
1 (<2,770)	2,170	95	1.00	Reference	191	1.00	Reference	111	1.00	Reference
2 (2,770–3,786)	3,281	85	0.86	0.64, 1.15	203	1.14	0.93, 1.39	76	0.83	0.62, 1.11
3 (3,787–4,988)	4,344	84	0.74	0.55, 1.00	154	0.93	0.75, 1.16	82	0.95	0.71, 1.27
4 (4,989–6,792)	5,777	83	0.72	0.54, 0.97	143	0.91	0.73, 1.13	50	0.63	0.45, 0.88
5 (>6,792)	8,577	109	0.87	0.66, 1.16	123	0.86	0.69, 1.09	55	0.77	0.56, 1.07
			p for trend‡ = 0.52			*p* for trend‡ = 0.05			*p* for trend‡ = 0.06	
Retinol (μg)										
1 (<717)	545	93	1.00	Reference	141	1.00	Reference	73	1.00	Reference
2 (717–1,044)	875	106	1.07	0.80, 1.42	167	1.00	0.79, 1.26	60 0	0.80	0.56, 1.13
3 (1,045–1,481)	1,247	104	1.07	0.80, 1.43	157	0.93	0.73, 1.18	81	1.15	0.83, 1.60
4 (1,482–2,138)	1,768	74	0.79	0.57, 1.08	185	1.15	0.92, 1.45	80	1.10	0.79, 1.53
5 (>2,138)	2,768	79	0.87	0.63, 1.19	164	1.02	0.80, 1.29	80	0.99	0.71, 1.38
			p for trend‡ = 0.09			*p* for trend‡ = 0.53			*p* for trend‡ = 0.67	
Serum β-carotene (μg/liter)										
1 (<99)	72	94	1.00	Reference	187	1.00	Reference	103	1.00	Reference
2 (99–147)	122	93	0.78	0.59, 1.04	162	0.85	0.69, 1.05	89	1.02	0.77, 1.36
3 (148–201)	171	84	0.67	0.50, 0.90	165	0.88	0.71, 1.09	66	0.87	0.64, 1.20
4 (202–290)	238	91	0.68	0.51, 0.91	151	0.84	0.68, 1.05	60	0.89	0.64, 1.23
5 (>290)	385	94	0.65	0.49, 0.88	149	0.86	0.68, 1.08	56	0.94	0.67, 1.32
			p for trend‡ = 0.02			*p* for trend‡ = 0.30			*p* for trend‡ = 0.56	
Serum retinol (μg/liter)										
1 (<484)	438	121	1.00	Reference	204	1.00	Reference	82	1.00	Reference
2 (484–547)	517	92	0.83	0.63, 1.09	195	0.99	0.82, 1.21	80	0.93	0.68, 1.27
3 (548–607)	577	104	0.98	0.75, 1.28	159	0.88	0.71, 1.08	71	0.83	0.60, 1.14
4 (608–684)	641	77	0.85	0.64, 1.14	145	0.84	0.68, 1.04	66	0.68	0.49, 0.95
5 (>684)	753	62	0.73	0.53, 1.00	111	0.70	0.56, 0.89	75	0.80	0.58, 1.11
			p for trend‡ = 0.08			*p* for trend‡ = 0.001			*p* for trend‡ = 0.07	

* Proportional hazards models include adjustment for age, years smoked, cigarettes per day, intervention (α-tocopherol and β-carotene supplement), supplement use (β-carotene and vitamin A), energy intake, cholesterol, and fat. For models with serum nutrients, models are identical minus the dietary intakes (energy, cholesterol, and fat) but including serum cholesterol.

† RR, relative risk; CI, confidence interval.

‡ Two-sided *p* for trend.

by smoking, smoking habits were modeled to best predict lung cancer, and years of smoking (duration) and cigarettes per day (intensity) were sufficient. However, since cigarette smoking is strongly related to patterns of nutrient intake (54), including fruit and vegetable intake, we cannot completely exclude the possibility that there is some residual confounding by cigarette brand (which may lead to different carcinogenic exposures) or use of filtered versus unfiltered cigarettes, for example. Although residual confounding by smoking, not uncommon in such studies, could theoretically contribute to the inverse associations, the relative homogeneity of this population of male smokers and the lack of an interaction with cigarettes per day argue against the possibility.

The strengths of this study include having up to 14 years of follow-up and 1,644 lung cancer cases, which greatly lessens the probability for the observed results to have been caused by chance. The potential for bias is reduced by the prospective nature of the cohort, with dietary information and

biospecimens obtained before the diagnosis of disease, and by the central review of the lung cancer diagnosis. Further, estimated carotenoid and retinol intakes in the diet were obtained using a detailed, validated modified dietary history questionnaire with a picture booklet aid (25).

Results of this study suggest that the consumption of several carotenoids from carotenoid-rich food sources is inversely related to lung cancer risk. Moreover, dietary lycopene was associated with stronger and more significant reductions in risk, and this association was slightly stronger than that observed for total fruit and vegetable intake. High fruit and vegetable consumption, particularly a diet rich in carotenoids, tomatoes, and tomato-based products, may reduce the risk of lung cancer, but dietary modification should not be considered a substitute for smoking prevention and cessation.

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